CHAPTER 29

Good Manufacturing Practice for Investigational Medicinal Products

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29.1 INTRODUCTION

The requirements and expectations for good manufacturing practice (GMP) compliance in the manufacture of investigational medicinal products (IMPs) within the European Union (EU) changed dramatically in 2004, with the implementation of the Clinical Trials Directive. Although the original European Commission Directive that lay at the heart of the GMP requirements in Europe (91/356/EC) limited its scope to those medicinal products that require a marketing authorisation, there have been EU guidelines on the manufacture of IMPs (Annex 13) for several years. This is in marked contrast to the situation in the United States, where the FDA requires that materials intended for use in a clinical trial are manufactured in accordance with the principles of GMP as set out in 21 CFR 211. There has been recognition, in practice, that full compliance with all the requirements is not practical, especially early in the development programme, but no formal guidelines for investigational product GMP has been published.

In the UK, this lack of any European legal basis for application of the requirements of 91/356/EC to materials without a marketing authorisation used in clinical trials resulted in a situation where the regulatory authorities expected that materials for clinical trial use were made in compliance with the principles of GMP, but they had no way of verifying that this was the case, or of taking action where it was not. In the UK, there was for some years a system of voluntary inspection, but this, of course, only dealt with organisations that were willing to volunteer.

The situation in other European countries was rather varied; some had quite tight regulation and inspection of clinical trial manufacturing operations, while others had more lax supervision. With the coming into force of the Clinical Trials Directive (2001/20/EC), both the GMP directive (91/356/EC, now renumbered as 2003/94/EC) and the Annex 13 guideline have been revised, GMP compliance became a legally enforceable requirement for the manufacture of IMPs. All IMP manufacturing sites will be inspected and licensed if found to be appropriately GMP compliant. At the time of writing (Summer 2004), some countries had still not fully implemented the directive, but this was expected shortly.

The GMP for IMPs should then be relatively simple and no different from the expectations for a licensed product, were it not for the nature of pharmaceutical development. The nature of

pharmaceutical development precludes the application of normal GMP controls for a number of good reasons:

- Particularly during the early stages of development, relatively little is known about the active pharmaceutical ingredient (drug substance). If it is a chemical entity, it is usually manufactured on a relatively small scale, with frequent changes in the synthetic route. Similarly, biotech products will be made initially on a small scale, using a process that has not been optimised, or even fully developed. Irrespective of its mode of production, the methods used to analyse the active pharmaceutical ingredient will be at a relatively early stage of their development. In many cases they will be restricted to the assay of the active pharmaceutical ingredient itself, with little-established ability to resolve either degradation products or impurities. To a great extent, this is all recognised by the GMP for active pharmaceutical ingredients (APIs, also commonly known as drug substances), ICH Q7A (incorporated into the EU Guide to GMP as Annex 18), in its section 19, ''APIs for use in Clinical Trials''.
- Information about active pharmaceutical ingredient properties will be limited. If development is well planned and executed, active pharmaceutical ingredients will have been made available for characterisation, stability and analytical development work, and a basic package of information to assist in the proper selection of the early dosage form will be available. All too often, however, a mixture of ignorance and cost cutting means that the information required is not available. This makes pharmaceutical development less soundly based.
- The drug product will also be at a very early stage of development; often a simple solution or a hand-filled capsule is all that can be produced as a result of limited drug supply.
- The analytical method for the drug product will normally be based on the method used for the active pharmaceutical ingredient itself, rather than be developed to meet the particular requirements of the dosage forms used in clinical trials. As a result, it is less reliable.
- Even Phase 1 trials, the very first administration of the drug to humans, may be carried out in a placebo-controlled double-blind study. In making materials for blinded trials, the manufacturer breaches one of the cardinal principles of GMP by producing two different products (active and placebo) that look as identical to one another as can be achieved. This completely reverses one of the most important and fundamental requirements of GMP, which is to be able to identify the product throughout its manufacturing life.

Individually, these differences create substantial problems for the quality management process. The combined effect of these is that, although the general requirements of GMP certainly apply to IMPs, GMP has to be re-interpreted and re-applied in the context of IMPs. The differences result in a unique set of responsibilities of the person releasing active pharmaceutical ingredient for the manufacture of IMPs as well as the IMPs themselves.

29.2 GMP FOR DRUG PRODUCT MANUFACTURE

This section of the chapter will concentrate on the differences between the requirements of full GMP and the requirements for IMPs as set out in Annex 13.

29.2.1 Quality Management

There can be no dispute that an IMP manufacturing operation needs a strong quality management system. Indeed, given the need for flexibility to deal with constant change, while retaining a full GMP ''state of control'' to assure continuing product quality and safety, the quality management system needs to be very strong.

There are many companies undertaking drug development that do not have the necessary manufacturing capacity and know-how, and therefore contract out this part of the work to a contract manufacturer. However, the original development organisation acts as the sponsor for the clinical trial itself.

The ICH GCP guidelines state that the study sponsor should ensure that the IMPs are manufactured in accordance with any applicable GMP. The knowledge and understanding of GMP issues of the study sponsor is often very different from that of the IMP manufacturer. The study sponsor may not have a strong quality management system. In many small organisations embarking on a drug development, quality management is at worst non-existent and at best limited. Small organisations developing one, or a few, new drugs do not have enough work in the early stages for full time quality personnel. This means that the sponsor organisation may not have the expertise, or understand the requirement, to assess GMP compliance by the contract-manufacturing organisation.

As a result, the sponsor organisation becomes entirely and yet unwittingly dependent on the quality management system of the contractor's quality management organisation.

The proper situation is that the quality management system within the study sponsor should comprehensively address the quality issues surrounding the analysis and release of active pharmaceutical ingredient and IMP alike. Where the organisation sponsoring the clinical study is not in a position to resource and execute this activity in its own right, it should use a properly qualified expert in IMP quality management to ensure that either

- a quality management system is (put) in place in the sponsor organisation, sufficient to control the manufacture and release of active pharmaceutical ingredient and IMPs

or

- the sponsor responsibilities under Annex 13 and the Clinical Trials Directive are wholly discharged by the contractor commissioned to prepare the IMP.

If the latter process is selected, it is incumbent on the expert to explain to the senior management team in the sponsor organisation, in simple and unambiguous terms, the nature of the sponsor's responsibilities, and the risks which they are taking by delegating responsibilities on, they do not fully understand themselves to a third party.

Nevertheless, delegation of the responsibility to the manufacturing contractor can only ever be part of the process. In the vast majority of IMP manufacturing activities, the active pharmaceutical ingredient will not be synthesised or analysed by the contractor manufacturing the IMP. The contractor may not, therefore, be able to release the active pharmaceutical ingredient as being suitable for human use as this requires, amongst other things:

- comparison of the analytical profile batch intended for human use with the active pharmaceutical ingredient used in toxicological testing,
- assessment of the significance of the differences between the human use and the toxicology batches and
- release (or rejection) of the active pharmaceutical ingredient as being suitable for use in humans.

In our experience, perhaps not surprisingly, this is not a responsibility that many contractors are prepared to take on. The contractor's qualified person (QP), assuming that one is nominated, will only be able to assess work carried out within the contractor organisation. In our view, the responsibility for releasing the active pharmaceutical ingredient for human use should lie within the sponsor organisation's quality management system, drawing on expert reports from suitable personnel both at the contractor and at the sponsor. The review and release process should be

documented in a standard operating procedure (SOP) within the sponsor organisation even if it is the only SOP in their quality management system.

29.2.2 Personnel

In the EU GMP, the chapter on personnel defines the duties of two key individuals, the Heads of Production and Quality Control (QC), and touches on the role of a third, the QP (who may be the Head of QC). In an IMP manufacturer, there may not be a person who, strictly speaking, is the Head of Production, but it is vital that the organisation examines the tasks allocated to this position and ensures that they are carried out by an identified individual or individuals. Given that there is usually less-known information about the drugs being developed and that the production and analytical processes may not be fully validated (see under "Validation"), the QC role may be larger than that normal for an established product, and the position of Head of QC is therefore more critical. The third individual mentioned, the Qualified Person, is a requirement that has been applied to licensed products for many years, but is new to IMPs. The role of the QP in dealing with IMPs is covered under "Batch Release".

Another major topic of this chapter is training. This is no less important for IMP production, although given that processes are being changed as development proceeds, the emphasis may be slightly different from that found in regular manufacturing. The first key aspect of training that must be addressed is ensuring that the staff has an appropriate knowledge of GMP. Skilled Development scientists sometimes see GMP as a straightjacket, restricting their creativity and slowing down the pace of their advance. It must be explained to them that while GMP compliance certainly does impose certain constraints and burdens, it is an essential tool in ensuring that the processes are reproducible, that the results generated are meaningful and that the product is consistent; all things essential for successful development as well as for the safety of the subjects who will be given the IMP. Formal training in equipment operation is also necessary, of course, but perhaps more than is normal for manufacturing staff, development personnel need a good understanding of problem investigation, deviation recording and change control.

29.2.3 Documentation

The fact that a process or product is being developed does not reduce the need for documentation. There need to be top-level policy documents setting out the organisation's approach to such topics as validation, cleaning and full SOPs for the operation of all facilities, equipment and systems. All steps in the manufacture and testing of IMPs need full records. This is often done by the use of pre-designed and authorised forms, such as the master-batch manufacturing record and forms used to collect analytical data. However, especially at the very beginning of development, changes are so frequent that pre-prepared forms may not be feasible. In this case, laboratory notebooks must be used to collect data. The advantage of this is flexibility, the disadvantage is that the amount of information recorded is not controlled as it is on a form. The only solution for this is to train staff in what must be recorded in their notebooks, and to require senior staff to check these notebooks frequently. The requirements for use of such notebooks should be very similar to those that apply to completion of forms, *i.e.* entries should be direct, immediate, legible and permanent, and entries should be signed and dated. Critical data should also be checked at the appropriate time, and such checks should be recorded in the laboratory notebook.

Another class of document required during development is specifications. In development, these are commonly set, and reviewed/revised, by a specification committee. This committee should include representatives of Regulatory Affairs, the group manufacturing the IMP, analytical development, QC and QA, and should be able to call on the support of a toxicologist and of people with clinical experience as needed. Specifications are necessary for raw materials, for critical

intermediates in the process and for the finished product. As has been mentioned repeatedly before, less is known about an IMP than a licensed product, and this has implications for all the specifications. First, it will not necessarily be known, early on, as to what are the critical indicators of material quality. This means that development specifications will tend to list many more test methods than will commonly be found later, and part of the development process is to review the test results periodically to determine which test methods are giving results that reflect the product quality. The other issue with specifications is of course the acceptance limits. Not all tests on a specification will, at first, have acceptance ranges; instead the results will be recorded "for information". However, for certain tests (of identity, strength and impurity levels) and tests relevant to safety (*e.g.* heavy metals, endotoxin and sterility), acceptance criteria are essential from the beginning of development for use in human subjects. While in some cases, the limits are obvious (there can be no dispute that a product claimed to be sterile should pass the sterility test, even though the material is an IMP), the acceptance ranges on other test methods such as impurity levels have to be set after much more thought, and these will need to be reviewed frequently to make sure that they are not too wide. This review should take into consideration not only the results for all batches of IMP tested to date, but should also consider process changes that may have effects on the results of, or even the need for, certain tests. The key batches that will influence the specification limits are those used in clinical trials, and those used in the toxicology studies. In setting initial limits, bear in mind that it is relatively easy to tighten specification limits, but a relaxation of limits must be thoroughly justified and carefully assessed.

Although we have said that the general documentation requirements for the production and testing of IMPs are similar to those that apply to licensed products, the GMP for IMPs requires that these be organised slightly differently than might otherwise be the case. To ensure that all the relevant documentation is available to the QP to allow proper assessment of a batch, Annex 13 identifies something called the Product Specification File. This does not need to be a physical file, but should allow rapid location of current versions of the following documents:

> *Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product.*
> *Manufacturing methods*
> *In process testing and methods*
> *Approved label copy*
> *Relevant clinical trial protocols and randomisation codes as appropriate*
> *Relevant technical agreements with contract givers, as appropriate*
> *Stability data*
> *Storage and shipment conditions*

(Taken from Annex 13, Revision 1 July 2003)

The key point about the Product Specification File, which also means that it requires quite intensive maintenance, is that it is only of value if it is up-to-date.

29.2.4 Facilities and Equipment

In general, although the facilities used to manufacture IMPs are often smaller than those used for licensed products, and are usually used to manufacture multiple products, the requirements of the GMP apply just as much as for a licensed product. All facilities and equipment must be appropriate for the purposes to which they are put, and must be appropriately qualified. Critical equipment (such as autoclaves for terminal sterilisation) must be periodically requalified; this should be considered for all equipment as part of the change control review process. In addition, it may be valuable to review all the changes to an item periodically, to evaluate whether a series of

minor changes, each alone not considered sufficient to require requalification, together add up to a need for requalification.

As mentioned above, the main difference, beyond scale, between routine manufacturing and IMP production, is that multiple compounds may be handled in the same plant. This requires that significant consideration be given to minimising the risks of cross-contamination, especially where equipment is not product dedicated. This puts a major emphasis on cleaning, of both the facility and equipment, and on the assessment of cleanliness. Formal cleaning validation as would be applied under normal GMP is not normally possible for several reasons. Firstly, not all the properties of the compounds handled will be known (so for example it may not be possible to establish the minimum or maximum human doses) and not all the toxicology work may have been completed. Secondly, the range of compounds handled means that different cleaning procedures may be required for different groups of compounds. Lastly, the fact that compounds are not handled in defined sequences means that the calculation of maximum allowable carry-over, where sufficient information exists (to determine whether the cleaning that has been carried out has been sufficient), has to be done every time. Furthermore, it is very unusual for a clinical-trial material to be manufactured in exactly the same way for three batches to enable formal validation of the method to be completed.

This means that there is a tendency to rely on an arbitrary limit, such as not more than 10 ppm of the previous compound in the smallest batch of the next product, and the routine verification of cleaning on a batch-by-batch basis. Evaluation of the cleaning verification during contractor selection is an extremely important part of the selection process. The simplest way to avoid verification problems is to use dedicated or disposable equipment. So, for example, many active pharmaceutical ingredient manufacturers use new glassware for the manufacture of each batch of small-scale synthesis of GMP materials. Likewise the use of dedicated product contact change parts, mixing bowls and utensils in product manufacture saves a great deal of analytical work and resource.

29.2.5 Production

The main differences in production operations, beyond the scale as mentioned above, are the need for frequent process changes, the relatively high occurrence of planned (and sometimes unplanned) deviations during production and the general lack of any knowledge on acceptable yields (which once again puts emphasis on rigorous cleaning and assessment of cleanliness). Process changes are handled through a change control system, just like equipment changes. More than these latter, perhaps, they require review by, amongst others, the regulatory affairs group to determine whether the proposed change necessitates notification of, or approval by, the regulatory authorities before implementation.

It is quite likely, particularly as processes are changed during the development programme, that deviations will occur, both planned and unplanned. It is very important therefore that an organisation that manufactures IMPs has a well thought and robust system for capturing deviations (Chapter 31), and for fully assessing their potential impact. The deviation record must also be included in the package of documentation reviewed by the QP at the time of batch disposition.

The requirements for retention samples of IMPs can be difficult to administer. Firstly, there is a requirement that samples of the starting materials (the active pharmaceutical ingredient and all recipients) are kept. Then, sufficient sample to repeat all the testing, twice, must be taken from the bulk drug products. This must be retained for at least one year longer than the expiration date of the IMP, which can be an administrative challenge if, as is common in early development, the expiration date of the IMP is extended (sometimes on repeated occasions) as a result of ongoing stability studies. Lastly, Annex 13 requires that samples of each batch of product should be kept, including blinded product. This means that for open label kits, the retention sample taken of the

bulk drug product may be sufficient. However, for blinded studies, it is necessary to retain samples of packed kits. The easiest way to do this, without destroying the blinding or randomisation, is to pack the kits in blocks, and to identify one block as intended for retention.

(*Note*: At the time of writing, a proposed Annex 19 to the EU GMP, covering ''Reference Samples and Retention Samples'' was under consideration. The first draft of this stated that the ''guidance may also be applied to investigational medicinal products, subject to any differences mentioned in Commission Directive 2003/94/EC, and any more specific guidance in Annex 13 . . .''. The draft did not appear to require any changes in the information given above, but the final version must be checked when published.)

In all cases, retention samples are only useful if they are kept under correct conditions. It is a requirement of US GMP that a sample of the retained material is examined visually at least once each year, looking for any obvious deterioration. Although this is not a requirement of EU GMP, and certainly involves some effort, it seems to the authors that this is a simple check to be carried out that might reveal a significant stability issue.

29.2.6 Quality Control

Again, the full requirements of the GMP guidelines apply to the testing of IMPs, their starting materials and intermediates. Analytical methods, however, may well be less developed, and may not be validated (see ''Validation''). Additionally, as mentioned in the section on specifications, under ''Documentation'', the product may well be less well understood than a licensed product, and it may well need more QC testing.

One question that may arise is the need for separation between analytical development and formal QC testing. There are, of course, arguments both for keeping these as separate groups and for putting them together in a single department. If they are separate, then analytical development is not constrained by the need to follow GMP, they are merely obliged to use sound scientific practices. Method transfer from the development group to the users in QC, although time consuming, presents a good opportunity to assess the robustness of the method. Additionally, method development is not slowed by the need to test batches of product. On the contrary, if analytical development and QC are together, there is no concern about method transfer taking time, of analytical development generating methods that are not suitable for routine use, and less need to duplicate expensive analytical hardware. The advantages and disadvantages are evenly balanced between the two models.

29.2.7 Contract Manufacture and Analysis

As mentioned above, it is quite common for the manufacture and/or analysis of IMPs to be contracted out. When this occurs, a properly constructed technical agreement is an essential document. For a manufacturing situation, the technical agreement must specify, in addition to specific details of the process, the specifications of raw materials, intermediates and the final product, and how these specifications should be reviewed and revised. It should cover GMP standards expected, and for manufacturing in a country outside the EU, should specify that the manufacture must be to a standard at least equivalent to that set out in directive 2003/94/EC. The agreement should also specify how deviations, and changes, are dealt with, whether the client will be notified and where client approval will be needed prior to implementation. Finally, the agreement must make it clear who is responsible for release of the product for clinical trial use. For agreements for analytical work, again, the agreement should set out the GMP standard expected and should describe how the results are to be reported. It should cover out-of-specification results handling, ensuring that both parties clearly understand what constitutes an out-of-specification result, what happens when one is encountered and who is notified, when and how. This may be done by references to agreed SOPs, or may be spelt out in detail.

29.2.8 Product Recall

This is perhaps better known as ''retrieval'', as it is the nature of most clinical trials that the sponsor knows exactly where drug is and should, in theory, be able to retrieve it relatively easily; whereas for a licensed product it can be distributed very widely, and the manufacturer alone does not have all the information necessary to ensure the product is traced to the individual patients. Irrespective of what it is called, it is essential to have a well thought-out procedure. A recall procedure is in some respects rather like a parachute, in that it is rarely used, but when it is needed, it must work. It is therefore important to test it periodically, at least as far as demonstrating that the organisation can, in an appropriately short time, account for all of a batch of IMPs and has the information and procedures necessary to notify quickly all the organisation and clinical trial sites that have received the affected product. In carrying out such mock recalls, however, great care must be taken to ensure that all staff know it is an exercise, so that there is no risk of a real recall being accidentally initiated.

29.2.9 Self-Inspection

This may be difficult in a small organisation, but having a disinterested look at your own organisation is a vital activity. The detailed process of such internal audits is not specified in the GMP, but it is not uncommon for a programme to require that each area of the company be looked at in turn over a one-year cycle. In general, regulatory inspectors will ask for evidence that a programme is in place and is being carried out, but will not ask to see individual audit reports, in case the writers of these reports will be constrained by fear that an inspector will use it to uncover issues in the company. Reports should therefore be clear on non-compliances and areas where compliance is weak; responses to internal audits should be required – these should describe what is to be done and when it will be done by. It is an essential part of the internal audit programme to keep top management aware of significant findings and of the progress of programmes to address them, as senior management allocate the company's resources.

As mentioned elsewhere, many organisations working in the drug-development area are small, and may find it difficult to maintain an up-to-date knowledge of changing regulatory requirements and expectations. Under these circumstances, internal audits could usefully be complemented by evaluation by an external party. A check by a suitably qualified and experienced outsider can be most valuable in pointing out areas of weakness that the internal audit programme may have missed.

29.2.10 Annex 13

This annex to the EU Guide to GMP is entitled ''Manufacture of Investigational Medicinal Products'', and it is sometimes erroneously thought of as the GMP for IMPs, at least within the EU. This is *not* the case; the annex describes the specific GMP requirements, *additional to or modifying* those set out in the rest of the Guide to GMP.

29.2.11 Validation

There is commonly a gradient of validation through the development of a drug, although different organisations tackle the need to have a validated process by the time the product is marketed in different ways. What follows is merely the opinion of the authors, and will need to be reviewed in the light of the properties of the drug and the nature of the disease being treated.

29.2.11.1 Before First Administration to Man. Any sterilisation process, and any other manufacturing process known to be critical to drug product safety, should be validated. On the analytical front, the sterility and endotoxin tests, and at least a test for identity an assay of potency,

and the test for impurities should be validated to the standards set in ICH Q2A, perhaps with the exception of robustness.

29.2.11.2 Development up to Phase III. Any other critical steps in the manufacturing process should be examined during this time, with the aim that the process used to manufacture Phase III materials (which will, one hopes, become the process used to make a licensed product) is shown to be at least validtable, if not actually validated.

All the analytical methods, at least for the finished product and the API, should be validated during this period as well.

29.2.11.3 During Phase III. The analytical methods applied to starting materials, other than the API, and to intermediates, should be validated during this period.

Cleaning validation work can also be done during this period, to ensure that a suitable cleaning process can be handed over to the routine manufacturing function at the appropriate time.

As for process validation, there is no requirement that this is completed by the time of submission of the Marketing Authorisation application. It must, however, be successfully completed by the time the product is placed on the market. Therefore, there is a case to be made for the completion of one validation run, prior to the submission, to verify both that the process is likely to be validated successfully and to verify that the validation protocols are appropriate. The remaining two (at least) validation runs can be carried out at a later date.

29.2.12 Batch Release

This is one of the areas most affected by the introduction of the Clinical Trials Directive, 2001/20/EC. The concept of QP certification is well established for licensed products, and the directive introduces a similar requirement for QP release of IMPs. To be a QP suitable for the release of IMPs, one either has to meet the current requirements for a QP as spelled out in Directive 2001/83/EC, or have been actively releasing clinical trial supplies prior to May 2004. (In the UK, a minimum period of 6 months prior to 1 May 2004 has been imposed, together with certain other requirements). In addition, the UK regulations require that the application to be named as a QP based on experience gained before 1 May 2004 has to be submitted prior to 1 May 2006. The duties of the QP are set out in the Clinical Trials Directive and in the national legislation implementing the directive, as well as in Annex 16 to the EU GMPs, although parts of this latter may need to be modified. For example, there is mention of testing upon importation in Annex 16. This is a requirement for licensed products made outside the EU in a country with which a mutual recognition agreement is not in place, which is incorporated into directive 75/319/EC and its later successor 2001/83/EC. There is no explicit requirement for such testing of imported IMPS in 2001/20/EC. However, it appears at the time of writing that the different member states may take differing approaches, some requiring testing on importation, others not, while yet others will decide on a case-by-case basis, dependent on the justification offered by the QP.

29.3 OTHER ISSUES

29.3.1 Active Pharmaceutical Ingredient Manufacture

A fairly recent development has been the creation of internationally-harmonised guidelines for GMP for the manufacture of APIs, as ICH Q7A ''Good Manufacturing Practice for Active Pharmaceutical Ingredients''. This has been incorporated into EU GMP as Annex 18. This is not currently enforceable under European law, but there are moves to change this, and to require compliance with this guideline in the manufacture of APIs. Control of API manufacture for

Clinical Trials use is set out in Section 19 of this guideline. This provides extensive guidance on what is required. In general the standards are similar to those one would expect to apply to the manufacture of drug product at a similar stage of development. The guidance is in some areas more detailed than that available for production of IMPs themselves and provides some useful insight into requirements for drug product manufacture as well. Some of the more challenging requirements are discussed below, with the extracts from the guideline given in italics.

29.3.1.1 Quality

> *A quality unit independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.*

This is an important principle, but one which is likely to present some challenges. As stated above, approval or rejection implies an assessment of suitability for use, and under full GMP is done against a comprehensive specification. In the case of IMPs, detailed specifications are unlikely to be available due to the limited data on the synthesis and analysis of the active pharmaceutical ingredient.

> *Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.*

The possible level of compliance with this requirement will depend on the nature of the raw materials used in the synthesis. This is recognised in a succeeding paragraph.

> *Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.*

The very nature of developing new compounds for evaluation in drug development takes the synthetic process into new areas of chemistry in which conventional standards of characterisation of starting materials will not be possible.

> *The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records or by other appropriate means. These documentations should include information on the use of production materials, equipment, processing and scientific observations.*

This seems to allow a suitable degree of flexibility while retaining the vital element of having a complete documentation record of what has taken place.

> *Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration and, where appropriate, equipment qualification assures API quality during this development phase.*

This is very similar to the principles applied to product manufacture.

> *While analytical methods used to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.*

The nature of the testing applied to active pharmaceutical ingredient for use in the manufacture of an IMP is worthy of discussion. In general, the vast majority of APIs for commercial production

are evaluated by high performance liquid chromatography (HPLC), using methods of exquisite sensitivity and resolution power. A basic HPLC method should be available for active pharmaceutical ingredient analysis for IMP use, but the normal degree of sophistication is rarely available. Additional more sophisticated testing should therefore be performed to assure product quality including ^{1}H and ^{13}C NMR, LC-MS and elemental analysis together with sulfated ash, organic volatile impurities (OVI), and any testing for any heavy metals used as catalysts at any stage of the synthesis. Melting point, normally by DSC, X-ray powder diffraction and IR spectra will provide further valuable information for later phases of development and are routinely performed in most companies.

Taken together, these tests provide both assurance of the nature and quality of the active pharmaceutical ingredient, and a suitable basis against which future batches can be evaluated. These tests should be applied not only to material used for IMP production, but also at earlier stages including GLP toxicology studies. Although not strictly within the scope of this chapter, the quality evaluation of active pharmaceutical ingredient for GLP use is just as important as testing for use in IMPs.

> *A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.*

This is an extremely important requirement and yet one which is often overlooked. It is inevitable that the quality of active pharmaceutical ingredient will change with time during development. The general expectation is that it will improve. Analytical methods used to analyse the active pharmaceutical ingredient must also improve. For this reason, any regulatory submission including those made at the clinical trial stage should include a batch analysis table presenting all of the analytical data available on all active pharmaceutical ingredient batches manufactured. If the development reaches the stage of Marketing Authorisation, analysis of all batches used in toxicology will need to be compared with the analysis of the active pharmaceutical ingredient to be included in the commercial product. For this data to be meaningful, the analysis of the early phase batches should be done using the best method available and compared with the proposed commercial active pharmaceutical ingredient analysed using the same method. If no samples above the legally required minima (which cannot be used for such purposes) have been retained from the early phase materials, this is not possible!

The retained samples should be stored in such a way that their integrity is most likely to be maintained. In many cases, storage at low temperatures is advisable.

Expiry and retest dating . . . applies to existing APIs used in clinical trials. For new APIs . . . (it) does not apply in early stages of clinical trials.

Nevertheless in the opinion of the authors, stability data on the API to be used in any human study should be generated.

29.3.2 Phase One Material Manufacture – "Drug in a bottle"

Pressures on resources and timings are resulting in a new approach to the preparation of IMPs for use in Phase 1 – the so-called "drug in a bottle" administration. This is the extemporaneous preparation of a solution or suspension of the active pharmaceutical ingredient immediately prior to administration by staff in the Clinical Study Unit, using drug in a bottle provided by the study sponsor for the purpose.

Although attractive in some ways, there are numerous pitfalls in this approach. One of the most obvious is that it contradicts a *sine qua non* of the GMP, namely that the product is identified and assayed prior to administration. Using the "drug in a bottle" approach means that, at best, the

product is analysed after administration and at worst not at all. Such an approach reduces the administration to that used in animal testing. Further problems are that placebo matching using the "drug in a bottle" approach is much less straightforward, as the drug is in solution or suspension and so can be both seen and tasted.

A further issue is that, if the drug is administered as a suspension, there is sometimes doubt that a repeat administration under identical conditions could be achieved bearing in mind the limited characterisation of active pharmaceutical ingredient properties usually available for first administration. Establishing that a subsequent administration truly repeated the original experiment, despite using material with the same morphic form and particle size, could be highly problematic.

It is recommended that quality management issues surrounding this approach should receive considerable scrutiny from quality Personnel and sponsor alike. To quote Tolkien, "Short cuts make long delays".

29.4 CONCLUSION

Despite the difficulties and issues raised above, the general principles of GMP apply to IMPs, just as they do to licensed medicinal products. However, the specific application of some of the requirements requires more careful planning and control.